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Docket No.: 27519-0012US1

Inventor: Christopher P. Holmes et al.

NOVEL SPACER MOIETY FOR POLY(EHTYLENE GLYCOL)

MODIFIED PEPTIDE BASED COMPOUNDS

NEW SHEET

Synthesis of H-TAP-Boc molecule

Synthesis of Cbz-TAP

$$O \longrightarrow O \longrightarrow NH_2$$

$$(TAP)$$

$$Cbz-Cl, DCM$$

$$O \longrightarrow O \longrightarrow NH_2$$

$$(Cbz-TAP)$$

$$FIG. 1A$$

Synthesis of Cbz-TAP-Boc

Synthesis of Boc-TAP

FIG. 1C

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MODIFIED PEPTIDE BASED COMPOUNDS
NEW SHEET

Attaching Spacer to Peptide with C-Terminus

Peptide with free C-terminus:

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Attaching Spacer to Peptide with Free Side-Chain Acid

Peptide with free side-chain acid:

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NEW SHEET

PEGylation of Peptide, with mPEG-NPC

Peptide with TAP on C-terminus:

mPEG-NPC

FIG. 4B

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NOVEL SPACER MOIETY FOR POLY(EHTYLENE GLYCOL)

MODIFIED PEPTIDE BASED COMPOUNDS

NEW SHEET

PEGylation of Peptide, with mPEG-SPA

Peptide with TAP on C-terminus:

FIG.5A

mPEG-SPA

FIG.5B

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Inventor: Christopher P. Holmes et al. NOVEL SPACER MOIETY FOR POLY(EHTYLENE GLYCOL) MODIFIED PEPTIDE BASED COMPOUNDS **NEW SHEET**

Attaching Spacer and Synthesizing Peptide

IZ

peptide synthesis

solid phase

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NOVEL SPACER MOIETY FOR POLY(EHTYLENE GLYCOL)

MODIFIED PEPTIDE BASED COMPOUNDS

NEW SHEET

Synthesis of Peptide Dimer with Spacer, Attached to Resin Synthesis of TentaGel-Linker:

FIG. 7A

Synthesis of TentaGel-Linker-TAP(Boc)

FIG. 7B

Synthesis of TentaGel-Linker-TAP-Lys

FIG.7C

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MODIFIED PEPTIDE BASED COMPOUNDS
NEW SHEET

Synthesis of TentaGel-Linker-TAP-Lys(Peptide) 2

(TentaGel-Linker-TAP-Lys)

(TentaGel-Linker-TAP-Lys(Peptide)2)

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NEW SHEET

Cleavage from Resin

NH2

(Peptide Dimer with Spacer)

(TentaGel-Linker-TAP-Lys(Peptide)₂)

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MODIFIED PEPTIDE BASED COMPOUNDS
NEW SHEET

Oxidation

Dimeric peptide (XYZ) containing oxidized disulfide bonds

Dimeric peptide (XYZ) containing

reduced cysteine residues

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NOVEL SPACER MOIETY FOR POLY(EHTYLENE GLYCOL) MODIFIED PEPTIDE BASED COMPOUNDS

NEW SHEET

PEGylation of Peptide Dimer with Spacer, with mPEG-NPC

FIG.8A

FIG.8B

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NEW SHEET

PEGylation of Peptide Dimer with Spacer, with mPEG-SPA

FIG.9A

FIG. 9B

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NOVEL SPACER MOIETY FOR POLY(EHTYLENE GLYCOL)

MODIFIED PEPTIDE BASED COMPOUNDS

NEW SHEET

Ion Exchange Purification

FIG. 10

m=1-5, n=1-14, m and n are integers

FIG. 11A

$$X = OH$$
, $O-N$, $O-NO_2$, or $O-F$

FIG. 11B

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NOVEL SPACER MOIETY FOR POLY(EHTYLENE GLYCOL)

MODIFIED PEPTIDE BASED COMPOUNDS

m=1-5, n=1-14, m and n are integers

FIG. 11C

$$O = (CH_2)_m$$

m=1-5, n=1-14, m and n are integers

FIG. 12A

$$X = OH O-NO_2$$
 or $O \longrightarrow F$

FIG. 12B

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NOVEL SPACER MOIETY FOR POLY(EHTYLENE GLYCOL)

MODIFIED PEPTIDE BASED COMPOUNDS

NEW SHEET

m=1-5, n=1-14, m and n are integers

FIG. 12C

Synthesis of Homotrifunctional Molecules Branched homotrifunctional molecules having the structure

m=1-2, n=1-6, m and n are integers

$$X = OH O-NO_2$$
, or $O \longrightarrow F$

FIG. 13A

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m=1-2, n=1-6, m and n are integers

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NOVEL SPACER MOIETY FOR POLY(EHTYLENE GLYCOL) MODIFIED PEPTIDE BASED COMPOUNDS

NEW SHEET

C-Terminus Dimerization and PEGylation Using A Trifunctional Molecule A trifunctional molecule having the structure

FIG. 14A

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MODIFIED PEPTIDE BASED COMPOUNDS

FIG. 14B

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Inventor: Christopher P. Holmes et al.

NOVEL SPACER MOIETY FOR POLY(EHTYLENE GLYCOL) MODIFIED PEPTIDE BASED COMPOUNDS

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NEW SHEET

N-Terminus Dimerization and PEGylation Using A Trifunctional Molecule

FIG. 15A

FIG. 15B

FIG. 15C

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NOVEL SPACER MOIETY FOR POLY(EHTYLENE GLYCOL)

MODIFIED PEPTIDE BASED COMPOUNDS

FIG. 15D

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Inventor: Christopher P. Holmes et al.

NOVEL SPACER MOIETY FOR POLY(EHTYLENE GLYCOL)

MODIFIED PEPTIDE BASED COMPOUNDS

A trifunctional molecule having the structure

FIG. 16A

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Inventor: Christopher P. Holmes et al.

NOVEL SPACER MOIETY FOR POLY(EHTYLENE GLYCOL)

MODIFIED PEPTIDE BASED COMPOUNDS

(AcG)GLYACHMGPIT(1-nai)VCQPLRK-NH2

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NOVEL SPACER MOIETY FOR POLY(EHTYLENE GLYCOL)

MODIFIED PEPTIDE BASED COMPOUNDS

FIG. 16C

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NOVEL SPACER MOIETY FOR POLY(EHTYLENE GLYCOL)

MODIFIED PEPTIDE BASED COMPOUNDS

FIG. 16D